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(Article begins on next page)

Babies, Blemishes and FDA:

A History of Accutane Regulation in the United States

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The acne drug Accutane is one of the most dangerous products on the market today. The drug causes serious side-effects, most notably birth defects. Accutane is also one of the most effective prescription drugs available. This combination—unique efficacy coupled with unique risk—has posed a serious challenge for the Food and Drug Administration (FDA). Over the past two decades, FDA has grappled with how manage the completely preventable but persistently serious problem of Accutane-induced birth defects. On several occasions, the product spurred FDA to take unprecedented regulatory action.

In 1975 when American researchers for Hoffmann-La Roche began studying the chemical, isotretinoin, they were struck by its remarkable effectiveness.¹ The drug, which Roche Laboratories sells as Accutane, is an extremely powerful antidote to acne, unmatched by any other treatment. 85% of patients who take Accutane achieve full remission after a typical course of treatment (about five months).² Because of its exceptional power to cure acne, Accutane has been praised as a “miracle drug.”³ Just last year, FDA Consumer Magazine—FDA’s own magazine—pronounced the drug “the biggest breakthrough in acne drug treatment over the last 20 years.”⁴

This may seem like undue attention for a simple pimple remedy, but in actuality severe acne can be a seriously debilitating condition. A recent article in the Archives of Family Medicine noted, “Although acne is not a life-threatening disease, it has significant physical and psychological ramifications such as permanent scarring, poor self-image, social inhibition, depression and anxiety.”⁵ The type of acne indicated for Accutane treatment—severe recalcitrant cystic acne—is an extremely disfiguring condition caused by a chronic oil and gland disorder. Much more than the familiar blackheads, the condition is marked by tremendous pus filled lesions which typically spread

¹Accutane and Pregnancy, Wash. Post, Apr. 26, 1988 at A17.

²Robert S. Stern, A Uniquely Effective Drug Is Teratogenic: The Case of Isotretinoin, 320 New Eng. J. Med 1007 (1989).

³See e.g. Jennifer Frey, For the Stupaks, ‘Miracle’ Drug Casts a Light on Son’s Suicide, Wash. Post, Jan. 19, 2001, at C1.

⁴Michelle Meadows, The Power of Accutane, FDA Consumer, Mar. 1, 2001, at 18.

⁵Diane Thiboutot, New Treatments and Therapeutic Strategies for Acne, 9 Arch. Fam. Med 179, 179-180 (2000).

across the entire face and neck leaving behind pitted scars. One FDA official noted that the cysts can be so cosmetically crippling that people cannot get jobs.⁶ A patient described in the Journal of the American Medical Association (JAMA) became so displeased by his appearance that he dropped out of college.⁷ According to Jennifer Hansen, a 21 year-old taking Accutane who keeps an online Accutane journal, This medicine has given me my life back.... I am now confident, happy and very excited about life. I no longer feel inferior and can actually look people in the eyes.⁸

Since its release, Accutane has provided tremendous revenue to its marketer, Roche; the drug brings in over \$700 million a year for the Swiss company's prescription drug unit, Hoffmann-La Roche. About 12 million people worldwide (including 5 million Americans) have taken Accutane, which is called Roaccutane outside the United States.⁹ In 2000, Accutane sales totaled \$759.4 million—8% of total prescription drug sales.¹⁰

But as productive as it is, both as a money-maker and a therapy, Accutane also has the potential to destroy lives. Accutane is an extremely dangerous teratogen: it can cause severe birth defects when taken during pregnancy. About one quarter of babies born who have been exposed to Accutane during gestation have major congenital deformities. Those babies born without major malformations frequently develop severe learning disabilities. A whole segment of Accutane babies do not even survive pregnancy: 40% are spontaneously miscarried. Dr. Edward Lammer, a medical geneticist and consultant to FDA, describes the overall risk posed by Accutane:

This is an extraordinarily high absolute risk, really comparable, in terms of environmental exposures, only to Thalidomide or certain congenital infections. There is no other medication that poses an absolute risk anything remotely close to this, even medications used to treat cancer during pregnancy.¹¹

⁶Cristine Russell, FDA Steps Up Warnings to Doctors, Blood Banks on Risks of Acne Drug, Wash. Post, Mar. 30, 1984, at A1 (quoting Dr. Carnot Evans, an FDA medical officer).

⁷Acne Drug Depression Warnings Highlight Need for Expert Care, 279 JAMA 1057 (1998).

⁸Jennifer Hansen, Jenn's Accutane Journal, (2002) at <http://jmhpr.tripod.com/accutanediary/index.html>. There is no indication that Jennifer Hansen is affiliated with Roche's pharmaceutical company, Hoffmann-La Roche. The very fact that this young adult keeps a journal dedicated to her experiences with Accutane—and posts it on the internet—testifies to the power of the drug.

⁹Mary Duenwald, After 20 Years, Debate Over Drug Persists, N.Y. Times, Jan. 22, 2002 at F7.

¹⁰Roche's U.S. Patent for Accutane Expires, Wall St. J., Feb. 13, 2002, at B9.

According to Dr. Lammer, brain abnormalities are the most typical problem for Accutane babies, even babies who appear normal at birth (i.e. babies not counted in the 25%). In addition, Accutane commonly inhibits the development of the bones and cartilage of the face. Children may be born with no ears at all; sometimes there are small slits in the place of ears. Heart defects, which often grow fatal, characterize the third most common problem described by Dr. Lammer.¹² Many of the Accutane babies who do not suffer from congenital deformity have abnormally low IQ scores.¹³

Since its approval in 1982, references to Accutane have peppered the pages of law reviews and other publications. The drug has become an example for academics and others proposing reform.¹⁴ The popular media also have related the problem of Accutane babies episodically through the 19 years since Accutane-induced birth defects first appeared in 1983. But none of these accounts has offered a full history of Accutane in the U.S.

This paper takes a journalistic approach, tracing the chronology of Accutane in the U.S. in order to fill in the gaps of the story that has inspired so much controversy. Accutane has repeatedly pushed the frontier of FDA regulation, as the agency struggled to adapt its tools to meet the challenge of an extremely effective and extremely dangerous medication. By emphasizing the evolving American response to the high level of risk associated with Accutane, I hope to provide the material needed to evaluate the strengths and weaknesses of our current regulatory framework.

Discovery and Pre-Market Approval: 1970-1982

Perhaps the biggest challenge in chronicling Accutane has been to decipher the early history

¹²Id.

¹³Testimony of Dr. Jane Adams before the Dermatologic Drugs Advisory Committee, Sep. 18 2000, available at <http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3639t1a.pdf>.

¹⁴See e.g. Joan H. Krause, Accutane: Has Drug Regulation in The United States Reached Its Limits?, 6 J. L. & Health 1 (1992); Barry R. Furrow, Enterprise Liability for Bad Outcomes from Drug Therapy: the Doctor, the Hospital, the Pharmacy, and the Drug Firm, Drake L. Rev 377 (1996).

of the drug. Most of the information about Accutane’s development, testing and approval only began to emerge ten years after the drug reached the market. Creating a narrative has required piecing together fragments of the puzzle which surfaced over the course of the past decade.

One might blame Roche: the company has repeatedly gone to court demanding that material describing the development of Accutane be kept private.¹⁵ Of course, all manufacturers have the right to maintain confidentiality of trade secrets. But some believe that the Roche exploits that authority in order to keep certain details—details which might reflect poorly on the company—obscured.¹⁶ Questions about Roche’s disclosure practices recur throughout for the Accutane story.

Dr. Werner Bollag first studied the chemical compound, 13-cis retinoic acid at Roche laboratories in Switzerland during the 1960s. Bollag tested the compound as a treatment for skin cancer, and in 1971, discovered the drug’s ability to cure acne. But Bollag also realized that the drug could cause serious birth defects. The compound derived from vitamin A, a known teratogen. When it proved ineffective as a cancer therapy he abandoned the project. In a frequently quoted article from *Retinoids Therapy*, Bollag explained, “At that time [the 1970s], in the psychological climate engendered by the thalidomide tragedy, it would be inconceivable to develop an agent with teratogenic properties for the treatment of such a common complaint as acne.”¹⁷

In 1975, two scientists at the National Institutes of Health (NIH) started testing Hoffmann-La Roche’s 13-cis

¹⁵Hoffmann-La Roche v. Yoder, 950 F. Supp. 1348 (Ohio 1997); Hammock v. Hoffmann-La Roche, 622 A.2d 546 (N.J. 1996).

¹⁶The searches conducted by Frank Yoder, Mark Somerson, and the advocacy group Public Citizen are discussed below.

¹⁷Quoted in Diane Nygaard, Accutane: Is the Drug a Prescription for Birth Defects, *Trial*, Dec. 1988 at 81; Krause *supra* note 14, at 7.

retinoic acid (then known as isotretinoin) as a treatment for a severe skin disorder called lamellar ichthyosis. In their research, Drs. Frank Yoder and Gary Peck accidentally discovered that the chemical also cleared up acne. Subjects who had been covered with pimples returned to the office with clear skin.¹⁸ On November 27, 1976 Yoder and Peck published their findings in the British medical Journal, *Lancet*.¹⁹ According to the two doctors, Hoffmann-La Roche never informed them of Werner Bollag's work. "I didn't know about the 1971 studies until 1986," Peck later told the *Columbus Dispatch*, "My first reaction was that I wasn't sure that I believed it in the first place."²⁰ For years, Yoder and Peck believed that they were the first to discover the isotretinoin as an acne cure.

Isotretinoin became Accutane, and in clinical trials researchers carefully avoided exposing pregnant women to the drug. Hoffmann-La Roche had conducted animal studies, and offspring of subjects showed facial deformities much like the ones that have subsequently been seen in Accutane babies.²¹ Most test centers excluded women. Those researchers who did include women in trials required a negative pregnancy test and contraceptive use. In an affidavit, David Benjamin who monitored the clinical trials in 1977 and 1978 explained, "I felt that the risk of giving birth to a deformed child... was so great as to make it ethically improper and scientifically foolish to give Accutane to women who were not using an effective form of contraception." According to Benjamin, one woman involved in a clinical trial became pregnant, and the company urged her to have an abortion.²² When Roche submitted Accutane for FDA approval in July of 1981, the company reported that no human babies had been exposed to the drug.

FDA referred the application to the Dermatologic Drugs Advisory Committee, one of many panels of outside experts who provide FDA with independent recommendations about drug applications and other FDA poli-

¹⁸Mark D. Somerson, *Swiss Researcher Never Published Acne Drug Studies*, *Columbus Dispatch*, May 1, 1996, at 2C.

¹⁹Gary L. Peck and Frank W. Yoder, *Treatment of Lamellar Ichthyosis and Other Keratinizing Dermatoses with an Oral Synthetic Retinoid*, 2 *Lancet* 1172 (1976).

²⁰Somerson *supra* note 18.

²¹Nygaard *supra* note 17 at 81 (citing FDA's, *Summary Basis of Approval*, NDA 18-662, Jan. 15, 1982).

²²Mark D. Somerson and Jill Riepenhoff, *Patient was Urged to Get an Abortion; Researcher Feared Defects in Accutane User's Baby*, *Columbus Dispatch*, Apr. 8, 1996 at 1C (quoting Benjamin's 1994 affidavit for *Fetterolf v. Hoffmann-La Roche*, 651 N.E.2d 1309, (Ohio 1995)).

cies. FDA provides administrative support to the Dermatologic Drugs Advisory Committee, which includes several dermatologists, other medical experts and a consumer representative. FDA generally follows advisory committees' recommendations, though they are not binding.²³

In January 1982 the Dermatologic Drugs Advisory Committee suggested FDA approve Accutane. But the Committee also urged that the label be revised. In its application for Accutane, Roche had written "Teratogenicity was observed in rats at a... dose of 150 mg/day. In rabbits, a dose of 10 mg/day was teratogenic... and induced abortions. There are no adequate and well-controlled studies in pregnant women."²⁴ Roche suggested a pregnancy risk rating of C. There are five risk categories: A, B, C, D and X, and a rating of C indicates that "studies in animals have revealed adverse effects of the fetus and there are no controlled studies in women.... Drugs should be given only if the potential benefit justifies the potential risk to the fetus." FDA insisted that Roche upgrade the warning for Accutane and classified it as category X, which indicates that the risk to fetus clearly outweighs any possible benefit from using the drug during pregnancy.

25

Clearly, the absence of human birth defects was the direct result of Hoffmann-La Roche's testing conditions: all female participants were given pregnancy tests and contraceptives, and the one woman who did become pregnant aborted. Although FDA heightened the pregnancy risk rating for the drug, the original label did not suggest the careful precautions that Roche itself had used during clinical trials. Instead, the label noted the fact that there had been no evidence of birth defects in humans.²⁶

In May 1982, nine months after the application had been submitted, FDA announced approval of Accutane.

²³Information about FDA's advisory committees is available at the Center for Drug Evaluation and Research website, at <http://www.fda.gov/cder/audiences/acspage/index.htm>.

²⁴Quoted in Jill Riepenhoff and Mark D. Somerson, *Company Soft-Pedaled Accutane Tie to Birth Defects in 1982*, Columbus Dispatch, May 19, 1996 at 2D.

²⁵Testimony of Dr. Colonel Evans before the Dermatologic Drugs Advisory Committee, 37 (May 8, 1989) available at <http://www.fda.gov/ohrms/dockets/ac/accutane/29t1.pdf>.

²⁶Quoted in Krause *supra* note 14, at 17.

The drug had been classified “1A,” top priority, and awarded fast track approval. According to a Hoffmann-La Roche spokeswoman quoted in the *Washington Post*, Approval came through so fast that it came as quite a surprise to everyone. . . .” Caught off guard, Hoffmann-La Roche took an extra four months preparing to launch the drug. The United States was the first country to approve Accutane.²⁷

Early Marketing: 1984-1987

In September 1982, Accutane arrived to a warm welcome. “There has never been a drug like it” *Newsweek* reported.²⁸ *U.S. News and World Reports* stated that Accutane could clear up most cases of acne within a few months.²⁹ During the first six months of marketing, doctors wrote 200,000 prescriptions for Accutane—many more than even Hoffmann-La Roche had expected.³⁰

At the same time, some of the doctors who had studied the drug began to voice alarm. Dr. Henry J. Roenigk had been chairman of the dermatology department at Northwestern University and participated as a researcher for Roche during clinical trials. In May 1982—just as FDA granted approval—Roenigk published an article in the *Journal of Dermatology* about Accutane’s potential to cause birth defects.³¹ Dr. Frank Yoder, one of the two NIH scientists who had seemingly discovered the acne remedy, wrote a letter to *JAMA* in January 1983. “I wish to express my concern and anxiety over the potential tragedy that might arise from abuse and misuse of Accutane.... The potential toxicity of this drug has been seriously

²⁷Penny Chorlton, FDA Outpaced Firm on Acne Drug, *The Wash. Post*, Sept. 14, 1982 at A17.

²⁸Matt Clark, Now a Real Cure for Acne, *Newsweek*, Sep. 13 1982, at 56 (quoting Dr.. Eugene Farber, chief of dermatology at Stanford University School of Medicine).

²⁹Remedy for Acne, *U.S. News and World Report*, Oct. 11, 1982 at. 83.

³⁰Riepenhoff and Somerson, *supra* note 24.

³¹Quoted in Mark D. Somerson and Jill Riepenhoff, Drug Had A Reputation in Europe, Doctor Recalls, *Columbus Dispatch*, Apr. 27, 1996 at 1C.

under-emphasized.”³²

Hoffmann-La Roche reproached the scientists for releasing information obtained while working for the company. Yoder claims that he received a hostile phone call from Roche executives. According to him, Roche representatives ”angrily told me I should not be writing that sort of confidential information. I didn’t agree with them. I thought the public good must be served.” (Roche has not confirmed this account.) Shortly afterward the company sent letters to all scientists who had participated in clinical trials, stressing the confidentiality of information obtained during research sponsored by Hoffmann-La Roche. In a 1996 court case, a Roche employee testified, “An investigator had written an article, and we wanted to re-emphasize to all investigators that the information they received was confidential.”³³

Within a few months, Hoffmann-La Roche began receiving stories about of babies born with severe birth defects to women who had taken Accutane. In June 1983—nine months after the drug had been released—three cases were reported to Roche.³⁴ The Company quickly sent out a “Dear Doctor” letter, warning against the dangers of using Accutane during pregnancy.³⁵ That August, FDA published an article in *Lancet* describing 12 reported cases of “adverse pregnancy outcomes” attributed to Accutane.³⁶ Roche distributed red warning stickers to pharmacies for Accutane containers and mailed a second Dear Doctor letter to 500,000 physicians. The company also revised the drug label to include more information about birth defects and a more prominently placed warning.³⁷

In September 1983, the advocacy organization Public Citizen petitioned FDA to further adjust the Accu-

³²Frank W. Yoder, *Isotretinoin: A Word of Caution*, 249 JAMA 350 (1983).

³³Quoted in Mark D. Somerson and Jill Riepenhoff, *Doctor Defends his Articles*, Columbus Dispatch, Apr. 26 1996 at 1A.

³⁴Pregnant Women Given Warning on Acne Drug, N.Y. Times, Jul. 26, 1983, at A12.

³⁵Accutane and Pregnancy, *supra* note 1.

³⁶Franz W. Rosa, *Teratogenicity of Isotretinoin*, *Lancet* 513 (1983).

³⁷Testimony of Dr. Jonathon Wilkin before the Dermatologic Drugs Advisory Committee, 37 (Sep.18 2000), available at <http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3639t1a.pdf>.

tane label. Public Citizen's Health Research Group claimed that the drug's warnings were inadequate and consequently Accutane had been over-prescribed. The group demanded a boxed warning describing the possibility of birth defects, spontaneous abortions, Crohn's disease and several other serious health problems. In addition, Public Citizen asked FDA to require patient package inserts explaining the possible side-effects in non-technical language. FDA declined Public Citizen's requests.³⁸

In the first 18 months of marketing, about 400,000 patients took Accutane. By March 1984, Roche collected reports of 20 Accutane babies.³⁹ The Dermatologic Drugs Advisory Committee convened a meeting to address the problem.

On the Committee's recommendation, FDA had Roche further strengthen Accutane's warning about birth defects. The label explicitly suggested that patients use contraceptives beginning a month before therapy. Roche also took out a "Medical Director's Page" in *JAMA* to inform doctors who might prescribe the drug. In addition, FDA advised blood banks to refuse donations from Accutane users. Although mild by today's standards, these controls were deemed "unprecedented regulatory action" by FDA spokesman William Grigg.⁴⁰

Between 1984 and 1988 Roche delivered seven more Dear Doctor letters warning about Accutane.⁴¹ In June 1985, FDA and Roche again upgraded the caution on the label, this time including a boxed warning as Public Citizen had requested in 1983.⁴² At that time, the boxed warning was the most serious directive that FDA employed, short of recall. Practitioners have suggested that FDA requires a black box warning when it

³⁸Larry Sasich, HRG Publication #1537, available at <http://www.publiccitizen.org/publications/release.cfm?ID=4899>.

³⁹Cristine Russell *supra* note 6.

⁴⁰*Id.*

⁴¹Jonathon Wilkin, *supra* note 37 at 36.

⁴²Larry Sasich, *supra* note 38.

hopes to decrease sales of a drug.⁴³ But in the years following the revision, Accutane prescriptions remained common and reports of severely deformed babies continued to surface.⁴⁴

Surviving the Risk of Recall: 1988-1995

In a private memo dated February 11, 1988 several scientists at FDA's Division of Epidemiology urged the agency to actively consider taking Accutane off the market. "All efforts to date have been unsuccessful at protecting against pregnancy exposure and the sequelae of birth defects and abortion." Based on studies of Michigan Medicaid patients, the authors, Drs. David Graham, Franz Rosa and Carlene Baum, estimated 900 to 1300 Accutane babies had been born in the U.S.⁴⁵ FDA had received reports of only 62 deformed babies.⁴⁶ In March, the Centers for Disease Control (CDC) released a report describing four New Jersey cases of multiple serious birth defects in babies exposed to Accutane before birth.⁴⁷ FDA scheduled a meeting of the Dermatologic Drugs Advisory Committee for the end of April.

On April 22, four days before the scheduled meeting, an account of the confidential FDA memo appeared on the front page of the *New York Times*.⁴⁸ Someone had leaked the document. News of the large estimated number of Accutane babies—combined with the large number of abortions suggested to have been caused by the drug—sparked a craze of media attention. Journalists questioned whether the manufacturer and doctors had pushed the drug too far and whether FDA had approved the drug too quickly.⁴⁹ New York Represen-

⁴³Raymond G. Mullady, *Everything You Needed and Wanted to Know About Black Boxed Warnings*, 68 *Def. Couns. J.* 50, 54 (2001).

⁴⁴See e.g. Edward Lammer et. al, *Retinoic Acid Embryopathy*, 313 *New Eng. J. Med.* 837 (1985).

⁴⁵Gina Kolata, *Anti-Acne Drug Faulted in Birth Defects*, *N.Y. Times*, Apr. 22, 1988, at A1.

⁴⁶Krause, *supra* note 14, at 20.

⁴⁷Accutane and Pregnancy, *supra* note 1.

⁴⁸Kolata, *supra* note 45.

⁴⁹See e.g. Philip J. Hiltz and Susan Okie, *Accutane: Recklessness or Reasonable Risk?*, *Wash. Post*, Apr. 26, 1988, at A17.

tative Ted Weiss publicly called on FDA to limit access to the drug. Weiss also questioned the agency's response, Why does the FDA proceed merely to schedule another advisory committee meeting?... We must not allow the advisory committee process to be used as an excuse to permit such a seriously birth-deforming drug to remain on the market.⁵⁰ A day later, Hoffmann-La Roche chimed in, indicting the Michigan study as "essentially meaningless" and calling the figures "grossly overstated."⁵¹ The company argued that the data had been obtained from too small a sample size for extrapolation and had been misinterpreted by FDA. Dr. Frank Yoder, by now no friend to Hoffmann-La Roche, gave a statement to the *Washington Post*, calling the company "negligent and wrong" for over-promoting the drug to doctors who were not dermatologists. Yoder also described the firm safeguards that had been in place during testing to ensure that no pregnant women were exposed to the drug. "It is incredible to require that in a study but not in a mass market situation.... This was very, very wrong." Hoffmann-La Roche officials "angrily dismissed" Yoder's charges.⁵² One source of controversy was the disparity between Accutane use in the U.S. and that in other countries. As of April 30, 1988 only three Accutane babies had been born in Europe.⁵³ A dermatologist in England commented, "The U.S. experience is one which horrifies us."⁵⁴ Most countries in Europe strictly limited access to the drug. In Switzerland, doctors had to register with the government to prescribe it. In the United Kingdom, only 350 dermatologist had authority to prescribe Accutane and only hospitals could dispense it. As a prerequisite to receiving the drug in Britain, a woman had to stipulate that she would be willing to have an abortion. Sweden never approved Accutane for general use; dermatologists applied for special permission when a patient had a particular need. In Spain, the Ministry of Health kept the name and address of every woman taking Accutane in a special registry. The European approach to Accutane reflected not just a different regulatory methodology, but also differing circumstances. In the wake of Thalidomide, Europeans

⁵⁰Quoted in Michael Abramowitz and Philip J. Hiltz, *FDA Eyes Ban on Acne Drug*, *Wash. Post*, Apr. 23, 1988, at A1.

⁵¹Phillip M. Boffey, *Maker of Drug for Acne Calls Birth-Defect Report "Invalid,"* *N.Y. Times*, Apr. 23, 1988, § 1, at 1.

⁵²Abramowitz and Hiltz, *supra* note 50.

⁵³Linda Amster, *Saturday News Quiz*, *N.Y. Times*, Apr. 30, 1988, § 1, at 14.

⁵⁴Quoted in Gina Kolata, *Europeans Placed Stiffer Curbs on Acne Drug*, *N.Y. Times*, Apr. 28, 1988, at A1.

treated all teratogenic drugs extremely cautiously. According to the British dermatologist quoted above, “As a group of doctors who lived through Thalidomide, we are much more careful about using Accutane.”⁵⁵ Advocates such as Public Citizen pointed to the low number of Accutane-related birth defects abroad as evidence of the need for restricted access.⁵⁶

The Committee meeting on April 26th was just as contentious as the public debate that preceded it.⁵⁷ One spectator remarked that the doctors had clearly divided into two camps: the dermatologists versus the pediatricians.⁵⁸ Everyone agreed that Accutane caused birth defects, but the dermatologists asserted that because it was so effective, and because treatment could be limited to a few months, the drug should remain on the market. Hoffmann-La Roche proposed an aggressive education program to reduce the risk of pregnancy. CDC’s Dr. J. David Erickson rejected this tactic, “the current approach... has failed.” He suggested the drug be dispensed only at a limited number of regional centers. Others from the Division of Epidemiology presented evidence that the drug was “markedly overprescribed.”⁵⁹ Ultimately, the Committee voted 4-to-3 to keep Accutane on the market but with restricted access. The Committee recommended that only a limited number of certified physicians be permitted to dispense the drug. In addition, women at high-risk of pregnancy would be required to procure a second opinion before receiving Accutane.⁶⁰

A month later, FDA announced that it would not follow the Committee’s recommendation to restrict access to Accutane. Questioning whether it had the authority to dictate who could prescribe the drug, FDA instead mandated new warnings for the label. The agency required that Hoffmann-La Roche provide informed consent forms to be signed by patients and doctors. In addition the FDA directed the company to double the type size in the warning; include a picture of a baby deformed by Accutane in the material going to patients;

⁵⁵Id.

⁵⁶Larry Sasich, *supra* note 38.

⁵⁷Transcripts available at <http://www.fda.gov/ohrms/dockets/ac/accutane.htm>.

⁵⁸James L. Mills, Protecting the Embryo from X-Rated Drugs, 333 *New. Engl. J. Med.* 124, (1995).

⁵⁹Transcripts from the Dermatologic Drugs Advisory Committee, Apr. 26, 1989, available at <http://www.fda.gov/ohrms/dockets/ac/accutane.htm>.

⁶⁰Michael Abramowitz, FDA Advised to Limit Accutane Prescriptions, *Wash. Post*, Apr. 27, 1988, at A1.

dispense the drug in a blister-pack with warnings on every package; instruct doctors that they should give both written and oral warnings; add a symbol of a pregnant woman crossed out on the material given to doctors and patients; and conduct follow-up studies to determine the efficacy of the new program.⁶¹ Again, Accutane had pushed FDA to “an extraordinary new measure,” one which the agency itself described as “unprecedented,”⁶² and “a very dramatic and innovative approach.”⁶³

Hoffmann-La Roche announced that it would comply with FDA’s requirements. In addition, the company offered to pay the costs of contraceptive counseling and pregnancy testing for any woman receiving a prescription of Accutane.⁶⁴ Taken together Roche titled the new interventions its Pregnancy Prevention Program and implemented the changes in October 1988. Researchers at the Slone Epidemiology Unit of the Boston University School of Public Health were enlisted to study the efficacy of the program as dictated by FDA. Debates continued throughout 1989. On May 8, 1989, the Dermatologic Drugs Advisory Committee again met to discuss Accutane. The group accepted comments from representatives of Teratology Society of America, the Association for Retarded Citizens of the U.S., the March of Dimes, the Accutane Litigation Group, and the American Academy of Pediatrics among others. Dermatologists presented pictures of patients who had suffered from extremely severe acne and had been cured by Accutane. Epidemiologists at CDC expressed the “deep level of concern that we feel... about the ongoing very high rate of use.” Hours were spent arguing over the numbers. Committee members agreed that it was too soon to evaluate Roche’s success in reducing pregnancy—the Pregnancy Prevention Program was only six months old; FDA would continue to monitor the situation.⁶⁵

⁶¹Described in the transcripts from the Dermatologic Drugs Advisory Committee Meeting, May 8, 1989, available at <http://www.fda.gov/ohrms/dockets/ac/accutane.htm>.

⁶²Philip J. Hiltz, *Stong Birth-Defect Warnings to Be Required on Acne Drug*, Wash. Post, May 27, 1988, at A1.

⁶³Lawrence K. Altman, *Strict Curb Urged on Drug Linked to Birth Defects*, N.Y. Times, May 27, 1988, at A1.

⁶⁴*Id.*

⁶⁵Transcripts from the Dermatologic Drugs Advisory Committee Meeting, May 8, 1989, available at <http://www.fda.gov/ohrms/dockets/ac/accutane.htm>.

In the fall a fight broke out in the back pages of the New England Journal of Medicine. Robert Stern, a dermatologist in Boston, had written an article describing Accutane as a uniquely effective treatment for acne. He also described the birth defects caused by the drug and outlined Roche's new Pregnancy Prevention Program remarking on "the substantial burden" placed on physicians. Stern concluded, "Our success in facing the challenge of (Accutane) will be important in determining whether other [effective drugs that cause birth defects] become available and how they are used."⁶⁶ The September 14th issue of the New England Journal of Medicine contained several irate responses to Stern's piece. Sidney Wolfe and Andrew Holmes from Public Citizen lambasted Stern for neglecting to disclose his "substantial association with Hoffmann-La Roche," and suggested that numbers taken from the Slone Study were inaccurate. Likewise, Drs. Gerald Faich and Franz Rosa argued that there have probably been many more Accutane babies than have been reported. They lamented, "It is disappointing that little change has occurred in the rates of use of the drug in women, in spite of considerable publicity efforts to educate physicians." Stern replied noting that the New England Journal of Medicine had known of his connection to Roche (a fact verified by the editor-in-chief). He added, "I wrote the Sounding Board article because politics and polemics rather than scientific inquiry were dominating the debate about (Accutane)."⁶⁷

Eight months later the Dermatologic Drugs Advisory Committee met with the Fertility and Maternal Health Drugs Advisory Committee to discuss Accutane. FDA asked the two groups to address this question: had the pre-1988 adverse public health situation changed in a meaningful way and to a meaningful extent? The Committees found that it had not. The continued high level of Accutane use in the at risk population, prescriber non-compliance with important components of the program (many reproductive-aged women had not even been given a pregnancy test before starting therapy), and relatively low levels of participation in the Slone survey posed significant concerns for the group.⁶⁸ But the advisory panels decided to give Hoffmann-La Roche another seven months to prove the efficacy of the Pregnancy Prevention Program.⁶⁹

It actually took twelve months for the committees to reconvene—the joint meeting was held in May 1991—and by the time the groups came together, the¹⁵ media spotlight had disappeared. Unlike the previous three Accutane-related meetings, this one received no coverage in the Washington Post or the New York Times. Also in contrast to the earlier meetings, this one found that Hoffmann-La Roche's interventions achieved results. Committee members heard data from the Slone study indicating that number of fertile women taking Accutane

With that, Accutane fell out of the public eye and off of FDA's agenda. There would be no more Dermatologic Drug Advisory Committee meetings dedicated to Accutane in the 1990s. In 1995, the *New England Journal of Medicine* published the results of the Slone survey which seemed to suggest that the Pregnancy Prevention Program had succeeded. Just 402 of the 120,000 women who participated in the survey reported pregnancy. The survey tracked only about half of all women using the Accutane; consequently it could not be considered conclusive.⁷² Nonetheless, an editorial published alongside the article remarked that it provided “some encouraging news.”⁷³ It seemed the problem of Accutane babies would soon be over. Journalists and regulators turned their attention elsewhere.

Quieter Conflicts: 1992-1999

Out of the spotlight, Hoffmann-La Roche continued to grapple with the repercussions of Accutane related birth defects. By the mid 1990s, Accutane had earned the company a significant list of enemies, many of whom were looking to draw blood. Frank Yoder, in some ways a patron Saint of Hoffmann-La Roche—after all, his 1976 discovery had resulted in a tremendous money maker for the company—had spent the past fifteen years insulting Roche in the *Washington Post*. A subset of the plaintiff's bar called the Accutane Litigation Group had also been chipping away at Hoffmann-La Roche. The company had settled a number of expensive lawsuits. But each time documents were sealed, which meant new plaintiffs would have to start from scratch. The plaintiff's bar had become convinced that Hoffmann-La Roche had acted recklessly—something which might entitle clients to steep punitive damages. And the advocacy group, Public Citizen had been complaining vocally about Accutane since 1983. Over time, the group grew frustrated by FDA's complacency and convinced of Roche's culpability. In 1996, each of these three adversaries brought Hoffmann-La Roche to court.

On January 12, 1996 Dr. Frank Yoder sponsored an advertisement in a Columbus, Ohio newspaper *The Daily*

Reporter:

UNIQUE SEALED-BID AUCTION

The entire private collection of Frank W. Yoder M.D. regarding the development, use and misuse of ISOTRETINOIN (Accutane) will be sold by a sealed-bid auction.

This sale includes documents relating to the original protocol, letters from European investigators, and a never before distributed or published manuscript titled, Isotretinoin Birth Defects—A Preventable Tragedy.

Individuals, corporations and all other serious parties are invited to participate in this unique and one time event. The minimum bid is \$9.5 million dollars (U.S. Currency) and 20% of the net proceeds will be designated for the prevention of birth defects.

On February 11, a similar advertisement appeared in the Washington Post.⁷⁴

Roche promptly responded with service of process. The company sued Yoder in federal court, demanding an injunction against the auction and replevin of the documents up for sale. "Most of the documents involve trade-secret details of research and testing Hoffmann-La Roche performed before the drug was approved by the FDA for sale to the public," Roche's attorney Karl Seib said. "These trade secrets would be extremely valuable to Hoffmann-La Roche's competitors." Seib claimed that Yoder was trying to "intimidate and... threaten" the company into purchasing the material. (Yoder had called representatives from Roche to inform them of his auction several days before running the ad.)⁷⁵ Yoder argued that the material did not concern trade secrets, but rather Roche's culpability in cases of Accutane-related birth defects. In his brief for the court, Yoder's attorney wrote "Dr. Yoder's assemblage of information is unique in that it provides a road map to Roche's negligence and greed in the early marketing of Accutane. Such information is admittedly valuable to victims of Roche's inadequate early warnings."⁷⁶

⁷⁴Quoted in *Hoffmann-La Roche v. Yoder*, 950 F. Supp. at 1351.

⁷⁵Quoted in Robert Ruth, *Battle Opens Over Acne Drug Documents, Westerville Doctor Says Public Was Misled*, Columbus Dispatch, Mar. 21, 1996, at 1A.

⁷⁶Jill Riepenhoff and Robert Ruth, *Drug Firm Hid Accutane Data From FDA, Court Papers Say*, Columbus Dispatch, Apr. 1, 1996, at 1A.

Roche attorneys also appeared in another Ohio court in attempt to keep documents concealed from the plaintiffs' attorneys. In 1994, the Fetterolfs had filed suit against Hoffmann-La Roche for claims arising out of their son's Accutane-related birth defects. The Fetterolfs' attorneys had reviewed nearly 40,000 documents at Hoffmann-La Roche's New Jersey offices. On April 29, 1996 the plaintiffs petitioned the court to remove a protective order for an additional 9,000 documents. The plaintiffs suspected that the company had withheld information: they had been unable to find any correspondence between Hoffmann-La Roche employees in the United States and those who worked at the parent company in Switzerland. The plaintiffs supposed that the drug had caused birth defects during testing in Switzerland and that Roche had withheld the information from FDA and researchers in the U.S. Frank Yoder echoed this allegation when he testified in his own case on April 24th; he claimed that European trials of Accutane had been halted when they resulted in serious birth defects.⁷⁷

According to a Roche spokeswoman, the Company did not know for sure that Accutane caused birth defects until the first cases were reported in June of 1983. The chemical that Accutane is derived from, "has been known to be a teratogen since the '60s," the spokeswoman said, "That's why it was labeled category X when we launched. And that's why there were all of the stringent requirements during the trials."⁷⁸

Roche representatives testified that they'd refused access to the 9,000 documents because the Fetterolfs would not sign a protective order. Hoffmann-La Roche maintained that the order was necessary to protect the company's trade secrets. But unlike the victims who had preceded them, the Fetterolfs refused:

Hoffmann-La Roche has already been permitted to cause irreparable harm to many children by virtue of the tactics it employs to prevent dissemination of the truth. The consuming public is entitled to the truth, and (we) would urge this court to remove the cloak of secrecy which (Hoffmann-La Roche) attempts to hide behind.⁷⁹

The fate of Roche's secret documents would ultimately be decided by a third court in New Jersey. In 1986, the parents of Marvin Hammock sued Roche for Marvin's Accutane-induced deformities. When the parties settled

⁷⁷Jill Riepenhoff and Mark D. Somerson, Accutane Legal Fight Resumes, Columbus Dispatch, Apr. 24, 1996, at 1B.

⁷⁸Somerson and Riepenhoff, supra note 22.

the documents obtained by the Hammocks during discovery were sealed at the request of Roche. Public Citizen, intervened in the case challenging the decision to seal the documents. Initially, the Superior Court granted summary judgment to Roche. The case visited the appellate and trial courts twice more before arriving at the New Jersey Supreme Court. That Court highlighted the longstanding public policy of public access to information about health, safety and welfare, and held that the documents should be released unless Roche could show good cause for denying access to the public.⁸⁰ On May 9, 1996 the Hudson County Superior Court ordered the material unsealed. In announcing his decision to grant public access, Judge Gallipoli remarked, "Quite frankly... I don't think these documents amount to a hill of beans."⁸¹

Judge Gallipoli's assessment proved true: the documents did not provide the smoking gun that Public Citizen and plaintiffs' attorneys had expected. Records showed that within a year of releasing the drug to the market, company officials became extremely nervous about Accutane-related birth defects and that the first Accutane baby was born on April 29, 1983. A memorandum documented a telephone conversation between John Burns, vice president of research for Roche and Dr. Oakley at CDC: "Burns told Oakley that Roche would recommend that any woman exposed to Accutane during pregnancy have an elective abortion." In addition, the papers showed for the first time that Roche had submitted Accutane with a pregnancy risk rating of C, and that it had been FDA who insisted on upping the warning level. But the documents contained no evidence of communications between the New Jersey offices and researchers in Europe.⁸²

The following January, when Yoder won his legal battle, his \$9.5 million documents proved equally disappointing.⁸³

⁸⁰Hammock v. Hoffmann-La Roche, 622 A.2d 546.

⁸¹Quoted in Jill Riepenhoff, Judge: Acutane Documents Must Be Opened, Columbus Dispatch, May 10, 1996 at 3C.

⁸²Documents described in Riepenhoff and Somerson, supra note 24.

⁸³Hoffmann-La Roche v. Yoder, 950 F. Supp. 1348. The court concluded that Yoder's materials were not protected trade secrets, in part relying on the New Jersey court's order in Hammock. Because the material was publicly available it could not constitute a

Nothing in Yoder's collection provided concrete proof of Accutane babies born prior to 1983.⁸⁴

The most interesting material to surface during this period came from an Ohio newspaper, the Columbus Dispatch. The Dispatch was the only major publication that covered the series of Accutane-related lawsuits in 1996. As a result of Yoder's allegations, two reporters, Mark Somerson and Jill Riepenhoff, began their own investigation into the development and early marketing of Accutane.

The two were the first to report the confusion over who first discovered Accutane's ability to treat severe acne. Dr. Werner Bollag's role in the drug's history had been known since the 1983 publication of his article in *Retinoids Therapy*, but those who considered the subject wondered why Hoffmann-La Roche suddenly decided to reconsider Accutane as an acne treatment in 1975—four years after Bollag dropped his project. For example, Diane Nygaard chair of the Accutane Litigation Group had described Roche's decision to resume testing as "inexplicable."⁸⁵ Somerson and Riepenhoff uncovered part of an explanation: the company began testing again after Yoder and Peck independently realized that the drug could be used to treat acne and reported their success.

In addition, documents obtained through a Freedom of Information Act claim filed by Somerson reveal the extent to which Accutane had become a source of tension for FDA. Several members of FDA felt the agency should take a stronger position against Hoffmann-La Roche. David Graham, one of the authors of the controversial Michigan Medicaid study, criticized Roche's proposed labeling change in October 1988. The company had revised the label

secret. In addition Roche's failure to obtain a confidentiality agreement from Yoder in the 1970s undercut the company's claim.

⁸⁴In my research, I could not find any information about what Yoder did with his documents after winning his case. I did, however, make contact with Mark Somerson, one of the reporters who covered the story for the Dispatch. Having reviewed the files, Somerson commented that the collection did not contain "one memo or note that would show that the company knew that the drug caused birth defects." Email from Mark Somerson, Assistant State Editor, Columbus Dispatch, to Julia Green (Mar. 7, 2002, 15:37 EST)(on file with recipient).

⁸⁵Nygaard, *supra* note 17, at 81.

to read, "potentially all fetuses may be affected," and "physicians and patients should discuss the desirability of continuing the pregnancy." Graham suggested that Roche intentionally overstated the risk of birth defects. "The effect communicated by this wording to the patient and her physician is that there is virtually a 100 percent risk of severe birth defect and that induced abortion should be performed." According to Somerson's report, four doctors at FDA who tracked Accutane echoed Graham's concern: "Current product labeling serves Roche interests by reducing the number of women who deliver, and this reduces the probability that FDA will ever be informed of the exposure, because of massive underreporting.... The firm has not acted in good faith to truly and accurately answer questions relating to Accutane use in women and pregnancy exposure." Others at the agency felt it was important to convey a significant risk and that exposed fetuses should be aborted.⁸⁶

Somerson's report also portrays more explicit disputes within the agency. On May 8, 1989 a member of the Dermatologic Drugs Advisory Committee accused Graham of using "Nazi methods of decision-making" about Accutane. Meanwhile, Graham criticized the regulatory structure used by FDA.

It is troubling to realize the extreme lack of impartiality which characterizes this committee... Dermatologists prescribe the vast majority of (Accutane), and much of the problem with (Accutane) relates to its widespread use beyond the labeled indication.... It goes beyond normal expectations to believe that a committee of dermatologists would find fault with its own profession, or recommend that (Accutane) be removed from the market as an imminent hazard.... In this sense, presenting (Accutane) to the dermatology committee is somewhat akin to the notion of the fox in the henhouse.

For some members of FDA, the problem of Accutane-induced birth defects had presented fundamental questions about the agency's regulatory methods.⁸⁷

But the reporters were unable to uncover proof of Roche's actual knowledge of Accutane-induced birth defects

⁸⁶Mark D. Somerson, Memos Bare FDA Split Over Accutane, Columbus Dispatch, Jul. 14 1996, at 7C.

⁸⁷*Id.*

prior to 1983. Eventually, Somerson and Riepenhoff abandoned their investigation.⁸⁸

Although Frank Yoder, Public Citizen, the Accutane Litigation Group and the Columbus Dispatch all failed to produce evidence establishing Hoffmann-La Roche had withheld data from FDA, the ordeal did uncover some questionable behavior. Why would Hoffmann-La Roche propose a pregnancy risk rating of only C for a product so dangerous that the initial investigator abandoned it? And why hadn't the company shared information about the earlier research with scientists in the U.S. studying the drug in 1975? Research done by the Dispatch could also raise concerns about FDA. Had FDA catered to the manufacturer instead of protecting the public? Or were a few members—obsessed by some sort of personal vendetta—stirring up unnecessary conflict at the agency? The information uncovered never congealed into enough of a story to attract mainstream attention. Outside Ohio, most Americans remained unaware of Hoffmann-La Roche's ongoing legal troubles. Consequently, the company and FDA escaped scrutiny.

Regulation Resumed: 1999-2002

In the past few years, FDA and other government entities have revisited Accutane, questioning whether even more should be done to protect against Accutane-induced birth defects. Although Roche's Pregnancy Prevention Program succeeded in maintaining a very low pregnancy rate (2.7 per 1000 women taking Accutane) the number of patients taking Accutane steadily increased after 1991. Between 1992 and 1999, the number Accutane prescriptions grew by 200%.⁸⁹ Although the risk of exposed pregnancy for any individual woman taking Accutane had decreased, the total number of Accutane babies remained constant because of increased use.

CDC signaled the renewed interest in Accutane babies on January 21, 2001 in Mortality and Morbidity Weekly Re-

⁸⁸Somerson, *supra* note 84.

⁸⁹Testimony from Dr. Amarily Vega to the Dermatologic Drugs Advisory Committee Meeting, Sep. 18, 2000, available at <http://www.fda.gov/ohrms/dockets/ac/accutane.htm>.

port.⁹⁰ The item, “Accutane-Exposed Pregnancies –California, 1999,” described a series interviews that CDC had conducted with 14 women in California who had recently reported Accutane-exposed pregnancies. The researchers initiated the study in order to “draw attention to the continued occurrence” of Accutane-exposed pregnancies and to “learn more about why these exposed pregnancies happened.”⁹¹

The study diagnosed several problems contributing to the exposures. Although all of the women interviewed knew that Accutane should not be used during pregnancy, none reported having seen all the components of the Pregnancy Prevention Program. Four women had not seen any of the educational material, aside from what was printed on the package. Most of the women interviewed did not use two forms of birth control—eight had not used contraception at all when the pregnancy occurred. And only ten women took pregnancy tests before taking Accutane. The study highlighted that doctors continued to ignore many of the requirements of the Pregnancy Prevention Program.⁹²

The CDC report also underlined the problem of overuse. At least half of the respondents reported that they did not have the severe, recalcitrant, nodular acne for which the drug is indicated. One woman described taking Accutane one week each month to prevent oily skin during her period. In part, the researchers linked increase use of the drug to advertising. Four of the respondents stated that commercials had contributed to their decisions to see a doctor.⁹³

Within two months, Hoffmann-La Roche announced a new intervention, the Targeted Pregnancy Prevention Program, which would be geared toward the 0.27% of women who had fallen through the cracks of the previous efforts. The program consisted of a new batch of labeling changes; for example, two pregnancy tests should be timed according to instructions and performed before starting therapy; doctors should call pharmacists with

⁹⁰Accutane-Exposed Pregnancies—California, 1999, 49 CDC MMWR Weekly 28 (2002).

⁹¹*Id.* at 28.

⁹²*Id.*

⁹³*Id.* Hoffmann-La Roche began direct-to-consumer print advertising in 1996 and added television and radio advertisements in 1997.

prescriptions (as opposed to handing written prescriptions to patients); and two safe and effective methods of birth control should be used. FDA approved the new label in May. Roche also planned to distribute educational packets for patients titled “Be Smart, Be Safe, Be Sure,” and to organize Continuing Medical Education classes for doctors who prescribed the drug. A video would be distributed for doctors to show patients about the risks, and Roche would reiterate the importance of monthly pregnancy testing and counseling. That spring, Roche distributed pregnancy tests to all doctors known to prescribe Accutane. The educational video for went out in June. And in July Roche began visiting individual prescribers to do office training.⁹⁴

On September 18, 2000 FDA called on the Dermatologic Drugs Advisory Committee for advice about Accutane. FDA’s Dr. Jonca Bull posed the question to the Committee. “From a risk management standpoint, can we in our mission to ensure the safe and effective use of drug products, given societal and regulatory realities, develop a framework that further reduces the known risk of teratogenicity attendant to the use of (Accutane.)” FDA asked the panel to consider which risk management tools should be used for Accutane and what next steps should be taken, if any, if improved risk management is not realized. The committee was to reflect on a variety of mechanisms—increased risk communication, modified packaging, restricted distribution, mandatory monitoring of patients, and improved informed consent—and formulate a general recommendation for FDA.⁹⁵

Hoffmann-La Roche presented data to the Committee suggesting that education would be the best way to reduce pregnancy. Roche had knowledge of 1,995 cases of pregnancy exposures to Accutane, 70% of which occurred after the initiation of the Pregnancy Prevention Program. Of those women an estimated 61% had been using only one form of contraception and 34% had failed to use contraception. 14% of the women were unknowingly pregnant at the initial visit with the doctor. This reflected a need for more information about the importance of multiple forms of birth control and pregnancy testing. Roche also presented figures that showed many doctors had

⁹⁴Testimony from Eileen Leach to the Dermatologic Drugs Advisory Committee Meeting, Sep. 18, 2000, available at <http://www.fda.gov/ohrms/dockets/ac/accutane.htm>.

⁹⁵Testimony from Jonca Bull to the Dermatologic Drugs Advisory Committee Meeting, Sep. 18, 2000, available at <http://www.fda.gov/ohrms/dockets/ac/accutane.htm>.

failed to comply with the Pregnancy Prevention Program, prescribing the drug without first testing for pregnancy or obtaining a signed informed consent. Presumably, outreach efforts could achieve improved doctor participation and fewer pregnancies.⁹⁶

The Committee also listened to the usual information about the dangers of Accutane exposure during pregnancy and about the drug's unique ability to cure acne. Dr. Lammer, one of the participants in CDC's 1999 Study, commented, "In terms of medications, in terms of the magnitude of risk and the severity of malformations, this drug is really unique." Dr. Barbara Reed, a member of the Board of the American Academy of Dermatology, described the risks associated with acne: "There is no single disease which causes more psychic trauma, more maladjustment between parents and children, more general insecurity and feelings of inferiority and greater sums of psychic suffering than does acne." It was a battle of superlatives.⁹⁷

A representative of Celgene, the U.S. manufacturer of Thalidomide, described the program that had been implemented with the release of that drug in 1998. Under the System for Thalidomide Education and Prescribing Safety (STEPS), Celgene required doctors and pharmacies to register with the company to prescribe or dispense the drug. In addition, all patients participated in a mandatory survey tracking their Thalidomide use. At that time, about 10,500 pharmacies and 900 doctors had enrolled in the program. Representatives from the Thalidomide Victims Association of Canada, the Organization of Teratology Information Services, the March of Dimes, and Public Citizen each pointed to STEPS asking the Committee require Roche to implement a similar program and restrict access to the drug. A representative from FDA's office of Postmarketing Drug Risk Assessment bolstered their case by belittling Roche's proposals; healthcare providers were not "lacking for the information or access into the information. It's putting it into practice that's the problem."⁹⁸

Dermatologists voiced objections to restricted access programs. Dr. Reed suggested that the system would disrupt

⁹⁶Transcripts from the Dermatologic Drugs Advisory Committee Meeting, Sep. 18, 2000, available at <http://www.fda.gov/ohrms/dockets/ac/accutane.htm>.

⁹⁷*Id.*

⁹⁸*Id.*

the doctor-patient relationship and force patients to find new doctors just to start a new treatment. Compelling patients to discuss sex and pregnancy with an unfamiliar doctor would undermine education efforts. Patients in rural communities might have to travel long distances to get needed care. Another dermatologist complained that the suggestion intruded too far into the profession, "As an individual practitioner, it was my decision that this patient be treated with Accutane, and it should remain my decision and not that of the manufacturer or pharmacist, or anyone else.... I am convinced that education... is the way to accomplish this."⁹⁹

The committee voted for a form of restricted access. In addition to increasing educational efforts, as Roche suggested, the Pregnancy Prevention Program should be modified: all prescriptions should be limited to 30 day-supplies, and before dispensing Accutane, pharmacists should have to confirm that a negative pregnancy test has been documented. For women taking the drug, registration in the Program should be mandatory as should participation in the Slone survey. (Previously, participation in the survey had been voluntary, and Committee members worried that the data were inaccurate.) The Committee also recommended that Roche be required to conduct independent surveillance to identify pregnancy exposures.¹⁰⁰

In a Dear Doctor letter, dated January 9, 2001, FDA announced that educational efforts had not succeeded in eliminating Accutane-exposed pregnancies: "... human memory is not an adequate precaution for managing severe risk." The Committee had recommended "additional systematized measures to manage risk and fully inform patients." FDA stated that it was working closely with Roche to address the recommendations that were made by the advisory committee.¹⁰¹

Nine months later, in October 2001, FDA revealed SMART (the System to Manage Accutane Related Teratogenicity). The new program, which takes effect on April 10, 2002 will require prescribers to study the SMART "Guide to Best Practices," provided by Roche and then send a signed "Letter of Understanding" to the company

⁹⁹Id.

¹⁰⁰Kenneth Lyons Jones, Jane Adams, Christina Chambers, J. David Erickson, Edward Lammer and Janine Polifka, *Isotretinoin and Pregnancy*, 285 JAMA 2081 (2001).

¹⁰¹Letter from Janet Woodcock, Center Director, Center for Drug Evaluation and Research to Health Care Providers (Jan. 9, 2001) available at <http://www.fda.gov/cder/drug/infopage/accutane/accutane-ltr.htm>.

certifying knowledge of how to prevent fetal exposure. Upon receipt of the letter, Roche will send prescribers yellow qualification stickers. All prescriptions for Accutane should have attached a special yellow sticker, which indicates that the patient has had a negative pregnancy test and counseling about pregnancy prevention. The pregnancy test will be repeated every month before a new prescription is provided. Pharmacists will only be permitted to fill prescriptions that have the yellow sticker. In addition, all female patients must be given the opportunity to participate in the Slone survey. Participation will not be mandatory.¹⁰²

It remains to be seen whether SMART will accomplish the goal of eliminating the tragedy of Accutane babies. Clearly, the program was designed as a compromise between the desire for European-styled programs which achieve very low rates of pregnancy exposure by strictly limiting access, and the conflicting goal of easy availability of medicine to those who need it. But, while the program may look like a form of restricted access—after all, only doctors with special yellow stickers can prescribe the drug—in actuality the new protections more serve as hoops to jump through than barriers to access. Any doctor can send in a Letter of Understanding and obtain the stickers; qualification is not limited to dermatologists or other healthcare providers with special training. And like the Letter of Understanding, the sticker itself amounts to nothing more than a statement by a doctor of self-certification. Conspicuously absent from SMART are any interventions designed to address the problem of overuse. The yellow sticker signifies that a patient has received pregnancy tests and counseling, not that a patient has severe cystic acne. Clearly, SMART caters to the concerns expressed by dermatologists at the September 2000 meeting: whether or not a patient obtains a prescription to Accutane remains almost entirely in the control of the physician.

A few modifications might have given this certification-based form of restricted access more teeth. For one, Roche might have made its half-day continuing medical education class a mandatory prerequisite for certification instead of a recommended event. In that way, the company would have ensured that doctors who receive stickers actually

¹⁰²FDA Talk Paper, FDA, FDA Announces Changes to the Risk Management Program to Prevent Birth Defects Caused by Accutane (Oct. 31, 2001) available at <http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01113.html>.

have been informed of the best practices. Similarly, FDA might have followed the Committee's recommendation and required actual documentation of two negative pregnancy tests—instead of just a yellow sticker. Then it would have been impossible for a doctor to prescribe the drug if he forgot to perform a pregnancy test. In order to write a prescription without performing two tests, a doctor would have to actively forge the documentation. At very least, FDA might have included a diagnosis of severe, recalcitrant acne as one of the preconditions for using the yellow sticker; this would have sent a clear message that Accutane was not appropriate for off-label use. As it stands, doctors are their own gatekeepers, and their judgment and neglect remain unchecked.

That said, SMART clearly provides some added value to the existing system. Presumably, many doctors will actually read the Guide to Best Practices before submitting the letters and will benefit from the increased education. In addition the yellow stickers might serve as a reminder, triggering doctors to perform pregnancy tests and provide counseling. Taken together the yellow stickers and letter of certification might be interpreted as a contract, and doctors who use the stickers without the requisite protections might be liable for their actions.¹⁰³ Or perhaps the yellow stickers will form the basis for malpractice liability. The precautions signified by the sticker suggest a clear standard of care required for the profession. Maybe the specter of the litigation that might arise from misuse of the stickers will be enough to scare doctors into compliance. More generally, the very fact of such a novel program will undoubtedly convey the message that Accutane poses serious risks and should not be prescribed casually.¹⁰⁴ Over the next few months, we will discover whether this mild form of restricted access proves enough to capture the remaining pregnancy exposures.

¹⁰³To succeed under this theory, plaintiffs would have to establish that they had been intended as third party beneficiaries of the contract with Hoffmann-La Roche, and consequently should be entitled to sue.

¹⁰⁴See generally Risk Management of Accutane, 287 JAMA 578 (2002) (“alerting physicians to the strengthened risk management program for isotretinoin”).

A Brief Sidebar: Accutane Linked to Suicide?

The primary focus of future of Accutane regulation may be mental illness. As of December 31, 2001, 140 Accutane users worldwide (94 in the U.S.) have killed themselves while taking Accutane or within a few months of stopping treatment. Another 257 patients have been hospitalized for severe depression or attempted suicide.¹⁰⁵ Many reported that the symptoms diminished or disappeared after stopping Accutane treatment; several patients found that when they resumed taking the drug, depression returned. Accutane ranks among the top 10 drugs in FDA's database with respect to depression and suicide reports.¹⁰⁶ But the number of reported cases among Accutane users is actually no greater than that in the general population. About 6.1% of persons age 15-24 have symptoms of severe depression in any given month.¹⁰⁷ And adolescents and young adults with severe acne may be particularly prone to depression.¹⁰⁸ This makes for a confusing situation: FDA has collected reports of patients who seem to suffer from depression only while taking Accutane, but there is no increased prevalence of depression in the overall population of users.

Perhaps because of its prior experiences, FDA has been quicker to require Hoffmann-La Roche warn about the possibility of depression and suicide, even in the absence of clear evidence. In June 1985 when FDA mandated a black box warning for Accutane, depression was included as one of the possible side effects that had been reported.¹⁰⁹ In 1997, based on case reports of serious psychiatric disorders, FDA approached Hoffmann-La Roche about heightening the warning. On February 24, 1998 Roche released a new label. The warning began:

¹⁰⁵Duenwald, *supra* note 9.

¹⁰⁶Diane K. Wysowski, Marilyn Pitts and Julie Beitz, Depression and Suicide in Patients Treated with Isotretinoin, 344 *New Eng. J. Med.* 460 (2001).

¹⁰⁷Acne Drug Depression Warnings Highlight Need for Expert Care, *supra* note 7, at 1057.

¹⁰⁸This is a point that Hoffmann-La Roche officials have been quick to point out. See e.g. Julie Brienza, Accutane Maker Warns of Suicide Danger in Patients, *Trial*, June 1988, at 90 ("Hoffmann-La Roche spokeswoman Kellie McLaughlin said teenagers traditionally suffer from a higher incidence of depression, making it difficult to determine whether the drug causes depression among its users. She added that the same hormones that contribute to the formation of acne can also contribute to depression").

¹⁰⁹The original black box warning is included on Congressman Bart Stupak's web site at http://www.house.gov/stupak/accutane_chronology.htm.

Psychiatric Disorders: Accutane may cause depression, psychosis and rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events.¹¹⁰

A month later, the United Kingdom required a similar warning. According to FDA, doctors should simply act as if Accutane causes suicide.¹¹¹

More recently, FDA and Hoffmann-La Roche have taken steps aimed directly at informing patients. In March 2001, Hoffmann-La Roche published a medication guide that explains the possible association between suicide and Accutane to patients. The company also unveiled a new informed consent form, which describes the concern about suicide and requires patients inform their doctors of any history of mental illness.¹¹² At monthly visits, doctors should check for signs of depression. This spring the company will send out a new brochure to dermatologists and other prescribing physicians instructing them how to recognize early signs of depression.¹¹³

But Hoffmann-La Roche has also indicated a familiar reluctance to disclose information. Only in July 1998, 14 months after FDA first approached Hoffmann-La Roche about adding suicide to the warning label, did the agency discover that a French study from 1994 showed an association between Accutane and depression. In March 1997, Roche had added “suicide attempt” to the warning label for Accutane sold in France. Hoffmann-La Roche never shared the information with FDA.¹¹⁴

In addition, Roche’s marketing demonstrated an insensitivity to the suicide concern. In 1998, about the same time that FDA required the risk of suicide appear on the label, Roche released a new advertisement for Accutane which included the following statement: “Effective treatment of severe recalcitrant nodular acne minimizes progressive physical scarring, as well as negative psychosocial effects such as depression and poor self image.” On March

¹¹¹Duenwald, *supra* note 9, (quoting Dr. Jonathon Wilkins, Director of Dermatology at FDA’s Center for Drug Evaluation and Research).

¹¹²Bernard A. Schwetz, *New Measures to Manage Risks Associated With Accutane*, 285 JAMA 1146 (2001).

¹¹³Rita Rubin, *From Acne Drug Maker, a Teen Depression Guide*, USA Today, Feb. 26, 2002 at 7D. This was one of the Dermatologic Drugs Advisory Committee’s recommendations in September 2000.

¹¹⁴Bart Stupak, *Accutane Chronology*, available at http://www.house.gov/stupak/accutane_chronology.htm.

5, 1998, FDA sent a warning letter to the company demanding the advertisement be pulled. According to the agency, “Statements in Roche’s promotional materials that Accutane therapy will minimize or improve the patient’s psychological status, including depression, are false or misleading and promote an unapproved use.”¹¹⁵ And like Accutane-induced birth defects, cases of suicide and depression have generated new adversaries for Hoffmann-La Roche—adversaries driven to take action. The international organization, “Roaccutane/Accutane Action Group,” formed in January, 1999. On its website the group describes the mission:

To demand the appointment of an independent national and coordinated international investigation into Accutane/Roaccutane and the manufacturers of the drug, its executives and key employees, concerning lack of safety standards, inadequate label warnings, knowledge of side effects concealed at launch of product, accuracy or inaccuracy of results disclosed in pre-trial studies, alteration and manipulation of data on side effects, applied by the manufacturers Roche from 1982 to date.¹¹⁶

One ally of the group is Michigan Congressman Bart Stupak. On May 14, 2000, Stupak’s 17 year-old son B.J. shot himself to death. B.J. had used Accutane, and a few weeks after his death the Stupaks discovered the link to depression. Since then, Bart Stupak has worked hard to publicize what he calls “spontaneous suicides,” suicides in seemingly happy people who take Accutane.¹¹⁷ Shortly after B.J.’s death, Stupak told his story on NBC’s “Today Show.”¹¹⁸ In addition, Stupak used his political position to pressure FDA and Hoffmann-La Roche to increase regulation of the Drug. It was Stupak who pushed the company to create an informed consent form and medication guide for patients; on Stupak’s urging Hoffmann-La Roche also terminated advertisements aimed at minors.¹¹⁹

Stupak’s case put Accutane on the Congressional agenda; on December 5, 2000, the House Committee on Gov-

¹¹⁵Wilkin, *supra* note 37.

¹¹⁷Frey, *supra* note 3.

¹¹⁸Ed Silverman, Acne Drug Concerns Head to Congress House Committee to Discuss Suicide Links to Accutane, N.J. Star Ledger, Aug. 15, 2001, at 29.

¹¹⁹Letter from Bart Stupak, Henry Waxman, Tom Barrett, Sherrod Brown, Marge Roukema, Tom Coburn, Zach Wamp and Ed Bryant, Representatives, U.S. House of Representatives, to Jane Henney, Commissioner, FDA and Patrick Zenner, President and CEO Hoffmann-La Roche (Oct. 11, 2000) (urging FDA to require informed consent form, medication guides, and no advertising to minors); Letter from Patrick Zenner, President and CEO, Hoffmann-La Roche, to Bart Stupak (Oct. 17, 2001) (informing Stupak that Hoffmann-La Roche would voluntarily implement all of the recommended changes). Available at <http://www.accutanelitigation.com/congress.htm>.

ernment Reform held a meeting, “Acne Drug Accutane & It’s Alleged Links to Depression and Suicide.” The Committee heard testimony from parents of teenagers who committed suicide while taking Accutane. Representatives from FDA, Hoffmann-La Roche, and the American Academy of Dermatology also participated.¹²⁰ A Congressional hearing was scheduled for October 2001 to probe whether Hoffmann-La Roche and FDA gave consumers adequate warnings about suicide. Congress postponed the hearing after September 11th.¹²¹ But in the aftermath of September 11th, one particular case brought the association between Accutane and suicide back into the spotlight. On January 5th, 2002 15-year-old Charles Bishop flew a small plane into an office building in Tampa, Florida. Investigators soon discovered a prescription for Accutane among Bishop’s belongings.¹²² Toxicology tests by the medical examiner found no Accutane in his blood, but his mother reported that Charles had taken the drug. Mrs. Bishop argued that Accutane might be responsible for her son’s behavior.¹²³ The copy-cat crime, coupled with a suicide note expressing sympathy for terrorists, garnered immediate coverage from all news media; newspapers throughout the country reported the association between Accutane and suicide.¹²⁴ According to an analyst quoted in the New Jersey Record, Accutane sales have dropped by ten percent since 2000 because of increased publicity of Accutane-linked suicides.¹²⁵ Undoubtedly, the association between Accutane and depression will continue to pose a problem for Hoffmann-La Roche. The manufacturer and FDA continue to struggle with this the highly publicized—but poorly understood—phenomenon.

Lessons to Learn

Without doubt, Accutane is a special drug, one that poses extraordinary challenges for FDA. Nonetheless, FDA’s

¹²⁰Transcript available at <http://www.accutaneaction.com/>

¹²¹Silverman, *supra* note 118.

¹²²Duenwald, *supra* note 9.

¹²³Keith Morelli, Final Report Details Boy’s Suicide Flight, Tampa Tribune, Mar. 13, 2002, at 1.

¹²⁴See e.g. Carolyn Susman, Accutane Link to Suicide Unconfirmed, Palm Beach Post, Jan. 30, 2002 at 3D; Debra Rosenberg, A Troubled Teenager’s Tragic Final Flight, Newsweek, Jan. 21, 2002, at 40; No Drugs Alcohol Found in Pilot’s Body, Milwaukee J. Sentinel, Jan. 17, 2002 at 10A.

¹²⁵Lewis Krauskopf, Hoffmann-La Roche’s Petition Means Generic Accutane Faces Delay, Record, Feb. 23, 2002, at 3 (quoting Denise Anderson an analyst with Bank Julius Baer in Switzerland).

experience with Accutane highlights several structural weaknesses in the overall regulatory system. In addition, Accutane's impact extends beyond the patients who have taken it and the company that markets it. By pushing FDA to devise new control techniques, Accutane left its mark on the agency. Although the drug itself remains unique, the story of Accutane provides insight into drug regulation in the United States generally.

It is also worth noting how much of the story has been driven by circumstance. For example, the United States' relative eagerness to approve Accutane must be explained in part by our inexperience with Thalidomide. Had more babies been deformed by Thalidomide—as they were in Europe—fewer would have been exposed to Accutane. Happenstance, like the fact that one teen suicide invoked terrorism or that another was the son of a Congressman, earned tremendous publicity for the potential association between Accutane and depression. Bart Stupak's position in the House of Representatives enabled him to effect marketing changes within a week. And politics have influenced regulation in other ways as well. For example, the controversy surrounding Accutane in the eighties in part derived from the product's relationship to abortion, a politically sensitive issue. In considering where to point fingers in the Accutane story, we should remember that some portions must be owed to fortuity. If we conceive of FDA as a safety net designed to protect consumers, then perhaps Accutane babies might be said to have fallen through the holes. The story of Accutane exposes many of FDA's vulnerabilities. For one, FDA has no authority over doctors or patients, the two groups who ultimately control whether a fetus will be exposed to Accutane. A clear conclusion to be drawn from this story is that Dear Doctor letters and warnings on labels do not effect significant change on the part of healthcare practitioners. This inability to control directly the gatekeepers to prescription drugs poses a real limitation for the agency. Products whose safety depends on behavioral practices will inevitably reach beyond the scope of FDA.

The story also raises fundamental concerns about the advisory committee system put in place by FDA. Are the doctors who would use a particular drug well-suited to decide whether it should be allowed on the market? Accutane provides revenue not only for Hoffmann-La Roche but also for the doctors prescribing it, most of whom

are dermatologists. (Each of the five million Americans who have used Accutane visited a doctor to obtain a prescription.) FDA might consider whether the value added by specialists' relative expertise is offset by this conflict of interest.

In addition, the story exposes the limitations of liberalism, in particular the idea that educated consumers should be free to make their own choices—and to suffer the consequences. Accutane's dangers cannot satisfactorily be addressed through consumer warnings: the victims of Accutane, unborn babies, cannot participate in informed consent. When choices and consequences are not experienced by the same individual, the model no longer makes sense. Regulatory tools aimed at increasing information may not be adequate protections for third party victims. The Accutane story might be deemed either a triumph or a failure. In public health terms, FDA and Roche have succeeded in achieving tremendous change. As compared to the general population, the pregnancy rate of 0.27% in Accutane users is extremely low. A country, such as ours, that has been unable to effect simple behavioral modifications, such as flossing, must admire the accomplishment. On the other hand, FDA's regulations and Roche's own interventions have collectively been unable to eliminate Accutane babies. Accutane-induced birth defects remain a *preventable* tragedy.